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EXAMINER	
O FARRELL, THOMAS JOHN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,272	KIM ET AL.	
	Examiner	Art Unit	
	Thomas J. O'Farrell	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/15/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/04/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, claims 1-11 with species election of Fok I as the first restriction endonuclease and BstF5 I as the second restriction endonuclease in claims 6 and 7, in the reply filed on 11/15/2005 is acknowledged. The traversal is on the ground(s) that Groups 1 and 2 should be examined together because the response asserts that polynucleotides of Group 2 as claimed cannot be used in a materially different process. This is not found persuasive because the examiner maintains that the polynucleotides of Group 2 can be used to encode specific polypeptides. Additionally, the response asserts that the claimed polynucleotides of Group 2 are constructed to accomplish the claimed methods of Group 1 and therefore would necessarily identify art relating to the method of using those primers. This is not found persuasive because the examiner notes that any result of a nucleic acid database search of the SEQ ID NO:s recited in claim 13 of Group 2 that is a polynucleotide of the sequence recited in one of these SEQ ID NO:s would be art related to the claimed SEQ ID NO: but would not necessarily provide art on the methods of Group 1.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-11 are currently under consideration. An action on the merits follows. Claims 12-16 are withdrawn from consideration as being drawn to non elected inventions.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in the Republic of Korea on 10/18/2002 and 09/02/2003. It is noted, however, that applicant has not filed a certified copy of the 10-2002-0063832 and 10-2003-0061066 applications as required by 35 U.S.C. 119(b). Therefore, the instant application is given the effective priority date of the US filing date: 10/17/2003.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 recite ".....wherein said amplified target polynucleotide comprises a tyrosine-methionine-aspartate-aspartate (YMDD) site....". It is unclear how the polynucleotide could comprise the amino acids of the YMDD site. The examiner

suggests that the applicant amend the claim to recite that the polynucleotide sequence *encodes* the YMDD site.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> **(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.**

6. Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al. (herein referred to as Kim, 2003, Korean J. Genetics, vol. 25, pages 63-75, 03/2003).

Regarding claim 2 reciting "wherein said restriction fragment comprising two single-stranded fragment includes one mutation among two or more different mutations in only one of said single stranded fragment and all other mutations in the other said single stranded fragment" the examiner interprets the "one mutation" that is only on one single strand to be distinct from mutations of the complimentary base of the "one mutation" that is only on one of said single strand.

Kim teaches a method detecting polymorphisms of the codon for the M of the YMDD sequence of the DNA polymerase gene of hepatitis B virus (claims 8 and 9; see abstract of Kim). Kim teaches that this method entails creating BstF5I and FokI recognition sites flanking the polymorphic sites by PCR, digesting the PCR product with

FokI and BstF5I at 37 and 45 C to create a fragment composed of a single-stranded 7mer that has one polymorphic site of the codon and 13mer that has an additional polymorphic site of the codon, and analyzing the molecular weight of the fragments compared to control fragments by mass spectrometry (claims 1-9; see Figures 1 and 2, Table 1, and page 66, column 2, para 2, lines 5-7 of Kim).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al. (herein referred to as Stanton, W0 01/90419 A2, 11/29/2001).

Regarding claim 2 reciting "wherein said restriction fragment comprising two single-stranded fragments includes one mutation among two or more different mutations in only one of said single stranded fragment and all other mutations in the other said single stranded fragment" the examiner interprets the "one mutation" that is only on one single strand to be distinct from mutations of the complimentary base of the "one mutation" that is only on one of said single strand.

Stanton teaches a method of determining the identity of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (claims 1 and 2; see Figure 1 and page 40, all of para 3 of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (claims 1 and 2; see page 41, para 3, lines 4-7 of Stanton). Stanton teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (claims 1 and 2; see page 41, para 1, lines 3-5, and Figure 1 of Stanton). Stanton teaches in the example of Figure 1, that the resulting 8mer that does not contain the polymorphism of interest, contains the rest of the inserted nucleotides in this fragment via PCR (claim 2; see Figure 1 of Stanton). Stanton teaches that the

fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton).

Stanton does not teach in the above method of polymorphism analysis specifically how the mass spectrometry analysis of the single stranded fragments is to be performed. However, Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (claims 1 and 2; see page 96, para 4, lines 1-4 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to perform the mass spectrometry analysis of the single stranded fragments generated in the polymorphism determination method of Stanton by comparing the molecular weights of the single-stranded fragments that contain the polymorphism to the molecular weight of control fragments, where a difference in the molecular weights indicates the mutation in view of the teachings of Stanton. The ordinary artisan would have been motivated to perform the mass spectrometry analysis of the single stranded fragments generated in the polymorphism determination method of Stanton by comparing the molecular weights of the single-stranded fragments that contain the polymorphism to the molecular weight of control fragments, where a difference in the molecular weights indicates the mutation in view of the teachings of Stanton because Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to the fragment that contains another base at the same polymorphic site, which could be interpreted as a control fragment.

10. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton in view of New England BioLabs 2000-2001 catalog (herein referred to as NEB).

Stanton teaches a method of determining an allele of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (see Figure 1 and page 40, all of para 3 of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (see page 41, para 3, lines 4-7 of Stanton). Stanton teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (see page 41, para 1, lines 3-5, and Figure 1 of Stanton). Stanton teaches that the fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton). Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (see page 96, para 4, lines 1-4 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to perform the mass spectrometry analysis of the single stranded fragments generated in the polymorphism determination method of Stanton by comparing the molecular weights

of the single-stranded fragments that contain the polymorphism to the molecular weight of control fragments, where a difference in the molecular weights indicates the mutation in view of the teachings of Stanton. The ordinary artisan would have been motivated to perform the mass spectrometry analysis of the single stranded fragments generated in the polymorphism determination method of Stanton by comparing the molecular weights of the single-stranded fragments that contain the polymorphism to the molecular weight of control fragments, where a difference in the molecular weights indicates the mutation in view of the teachings of Stanton because Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site.

Stanton does not teach a method of detecting a mutation *specifically* by cleaving an amplified target using first and second restriction endonucleases under conditions in which the second endonuclease does not cleave the target and then cleaving the target under conditions where the second endonuclease cleaves the target (claim 3) or the method of instant claim 1 specifically where restriction endonucleases having different optimum temperatures are used (claim 4). However, Stanton teaches that there are other possible restriction enzyme combinations that can be used in the above method of genotyping taught by Stanton and that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site (see page 43, para 4, lines 1-6 of Stanton). NEB teaches a table of restriction enzyme

isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton (see page 192 of NEB). NEB also teaches that FokI is active at 37 C and that BstF5I is active at 65 C (see pages 202 and 203 of NEB). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to use the combination of BstF5I and FokI (claims 6 and 7), which have different optimal temperatures (claims 4 and 5), in the method of genotyping taught by Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active in view of the teachings of NEB. The ordinary artisan would have been motivated to use the combination of BstF5I and FokI (claims 6 and 7), which have different optimal temperatures (claims 4 and 5), in the method of genotyping taught by Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active because Stanton teaches that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site and NEB teaches a list of isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton.

11. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niesters et al. (herein referred to as Niesters, J. Med. Microbiol., vol. 51, pages 695-699, 08/2002) in view of Stanton.

Niesters teaches a method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B by amplifying a region of DNA including the YMDD motif and digesting with SfcI (see abstract and Figure 2 of Niesters).

Neisters does not teach a method detecting a mutation where the amplified target includes the YMDD motif of the DNA polymerase gene of hepatitis B *specifically* where the amplified target is contacted by two restriction endonucleases to generate at least one restriction fragment comprising two single-stranded fragments of 2-32 nucleotides each, wherein at least one of said single-stranded fragments contains a mutation sequence (claim 8). However, Stanton teaches a method of determining an allele of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (see Figure 1 and page 40, all of para 3 of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (see page 41, para 3, lines 4-7 of Stanton). Stanton teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (see page 41, para 1, lines 3-5, and Figure 1 of Stanton). Stanton teaches

that the fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton). Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (claims 1 and 8; see page 96, para 4, lines 1-4 of Stanton). Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform (see page 22, para 3, lines 5 and 6 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to improve the method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B taught by Neisters by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of control fragments in view of the teachings of Stanton. The ordinary artisan would have been motivated to improve the method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B taught by Neisters by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of

control fragments because Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform, and that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site.

12. Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niesters in view of Stanton, further in view of NEB.

Niesters teaches a method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B by amplifying a region of DNA including the YMDD motif and digesting with SfcI (see abstract and Figure 2 of Niesters).

Neisters does not teach a method detecting a mutation where the amplified target includes the YMDD motif of the DNA polymerase gene of hepatitis B *specifically* where amplified target is contacted by two restriction endonucleases to generate at least one restriction fragment comprising two single-stranded fragments of 2-32 nucleotides each, wherein at least one of said single-stranded fragments contains a mutation sequence. However, Stanton teaches a method of determining an allele of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (see Figure 1 and page 40, all of para 3 of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (see page 41, para 3, lines 4-7 of Stanton). Stanton

teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (see page 41, para 1, lines 3-5, and Figure 1 of Stanton). Stanton teaches that the fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton). Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (claims 3 and 9; see page 96, para 4, lines 1-4 of Stanton). Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform (see page 22, para 3, lines 5 and 6 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to improve the method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B taught by Neisters by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and comparison of the molecular weights of the polymorphic fragments to that of control fragment by mass spectrometry in view of the teachings of Stanton. The ordinary artisan would have been motivated to improve the method of identifying a mutation, Y204S, in the YMDD motif of the DNA polymerase gene of hepatitis B taught by Neisters by using the method of polymorphism detection which entails PCR

amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and comparison of the molecular weights of the polymorphic fragments to that of control fragment by mass spectrometry because Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform, and that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site.

Neisters in view of Stanton do not teach methods of detecting mutations in the YMDD motif of the DNA polymerase gene of hepatitis B *specifically* where the amplified target is cleaved using first and second restriction endonucleases under conditions in which the second endonuclease does not cleave the target and then cleaving the target under conditions where the second endonuclease cleaves the target (claims 3 and 9). However, Stanton teaches that there are other possible restriction enzyme combinations that can be used in the above method of genotyping taught by Stanton and that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site (see page 43, para 4, lines 1-6 of Stanton). NEB teaches a table of restriction enzyme isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton (see page 192 of NEB). NEB

also teaches that FokI is active at 37 C and that BstF5I is active at 65 C (see pages 202 and 203 of NEB). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to use the combination of BstF5I and FokI, which have different optimal temperatures, in the method of genotyping taught by Neisters in view of Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active further in view of the teachings of NEB. The ordinary artisan would have been motivated to use the combination of BstF5I and FokI, which have different optimal temperatures, in the method of genotyping taught by Neisters in view of Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active because Stanton teaches that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site and NEB teaches a list of isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton.

13. Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nguyen et al. (herein referred to as Nguyen, 1998, J. Med. Virology, vol. 54, pages 20-25, 01/1998) in view of Stanton.

Nguyen teaches the identification of mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV by amplification of this region and direct sequencing (see abstract, page 21, column 1, all of para and 4, and page 22, column 1, para 3, lines 12-14 of Nguyen).

Nguyen does not teach the identification of mutations in the 5 prime non-coding region of HCV *specifically* where the amplified target is contacted by two restriction endonucleases to generate at least one restriction fragment comprising two single-stranded fragments of 2-32 nucleotides each, wherein at least one of said single-stranded fragments contains a mutation sequence, and subsequent analysis of the molecular weights of the fragments (claims 1 and 10). However, Stanton teaches a method of determining an allele of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (see Figure 1 and page 40, all of para 3 of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (see page 41, para 3, lines 4-7 of Stanton). Stanton teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (see page 41, para 1, lines 3-5, and Figure 1

of Stanton). Stanton teaches that the fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton). Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (claims 1 and 10; see page 96, para 4, lines 1-4 of Stanton). Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform (see page 22, para 3, lines 5 and 6 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to improve the method of identifying mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV by amplification and direct sequencing taught by Nguyen by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of control fragments taught in view of the teachings of Stanton. The ordinary artisan would have been motivated to improve the method of identifying mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV using amplification and direct sequencing taught by Nguyen by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and

analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of control fragments because Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform, and that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site.

14. Claims 3 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nguyen in view of Stanton.

Nguyen teaches the identification of mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV by amplification of this region and direct sequencing (see abstract, page 21, column 1, all of para and 4, and page 22, column 1, para 3, lines 12-14 of Nguyen).

Nguyen does not teach the identification of mutations in the 5 prime non-coding region of HCV *specifically* where the amplified target is contacted by two restriction endonucleases to generate at least one restriction fragment comprising two single-stranded fragments of 2-32 nucleotides each, wherein at least one of said single-stranded fragments contains a mutation sequence, and subsequent analysis of the molecular weights of the fragments (claims 3 and 11). However, Stanton teaches a method of determining an allele of a polymorphic base that entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism (see Figure 1 and page 40, all of para 3

of Stanton). Stanton teaches that the restriction endonuclease recognition sites are designed such that they surround and/or span the polymorphic base (see page 41, para 3, lines 4-7 of Stanton). Stanton teaches that upon cleavage by the restriction endonucleases, small fragments generally less than 20 bases are produced and in the example of Figure 1, a fragment composed of a single–stranded 8mer and a 12mer containing the polymorphism is produced (see page 41, para 1, lines 3-5, and Figure 1 of Stanton). Stanton teaches that the fragments can be analyzed by mass spectrometry to identify the nucleotide at the polymorphic site (see page 41, para 2, lines 1 and 2 of Stanton). Stanton teaches that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site (claims 3 and 11; see page 96, para 4, lines 1-4 of Stanton). Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform (see page 22, para 3, lines 5 and 6 of Stanton). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to improve the method of identifying mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV by amplification and direct sequencing taught by Nguyen by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of control fragments in view of the teachings of Stanton.

The ordinary artisan would have been motivated to improve the method of identifying mutations, including a mutation at position –99, in the 5 prime non-coding region of HCV using amplification and direct sequencing taught by Nguyen by using the method of polymorphism detection which entails PCR amplification using primers flanking the polymorphic site where one primer introduces two restriction endonuclease sites that flank the polymorphism and subsequent digestion of the PCR product and analysis of the fragments using mass spectrometry by comparing the molecular weight of the polymorphic fragments to that of control fragments because Stanton teaches that this method of genotyping is robust, highly accurate, and inexpensive to set up and perform, and that the identity of a single nucleotide polymorphic fragment can be found by comparing the molecular weight of the fragment to a control fragment that contains another base at the same polymorphic site..

Nguyen in view of Stanton do not teach methods of detecting mutations in the 5 prime non-coding region of HCV *specifically* where the amplified target is cleaved using first and second restriction endonucleases under conditions in which the second endonuclease does not cleave the target and then cleaving the target under conditions where the second endonuclease cleaves the target. However, Stanton teaches that there are other possible restriction enzyme combinations that can be used in the above method of genotyping taught by Stanton and that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site (see page 43, para 4, lines 1-6 of Stanton). NEB teaches a table of

restriction enzyme isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton (see page 192 of NEB). NEB also teaches that FokI is active at 37 C and that BstF5I is active at 65 C (see pages 202 and 203 of NEB). Therefore, it would have been prima facia obvious to one of ordinary skill in the art the time the invention was made to use the combination of BstF5I and FokI, which have different optimal temperatures, in the method of genotyping taught by Nguyen in view of Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active further in view of the teachings of NEB. The ordinary artisan would have been motivated to use the combination of BstF5I and FokI, which have different optimal temperatures, in the method of genotyping taught by Nguyen in view of Stanton where the target would be cleaved at a temperature where one enzyme would be active but the second enzyme would not and then cleaved at the temperature where the second enzyme would be active because Stanton teaches that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry analysis or some other suitable means, and contain a polymorphic site and NEB teaches a list of isoschizomers including the FokI and BstF5I combination that cleave 9 and 2 nucleotides away from the same recognition site and would produce a fragment of the appropriate size for mass spectrometry analysis in the method taught by Stanton.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas O'Farrell whose telephone number is (571) 272-8782. The examiner can normally be reached Monday-Friday from 8:30 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Thomas O'Farrell
Examiner
Art Unit 1634

11/9/06

JEHANNE SITTON
PRIMARY EXAMINER
11/6/06